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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,909	10/29/2003	James B. Lorens	021044-005820US	9257

20350 7590 08/23/2006

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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,909	LORENS ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 12, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,27-45,53 and 54* is/are pending in the application.

4a) Of the above claim(s) *13,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-19,27-37,40-45,53 and 54* is/are rejected.

7)☒ Claim(s) *19 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/16/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

. DETAILED ACTION

Election

1. The Election filed 07/12/06 in response to the Office Action of 6/12/06 is acknowledged and has been entered.

Applicant's election with traverse of Group I, claims 1-18 and 27-45,and the species: Group A, *in vitro*; Group B, chemical effect; Group C, small organic molecule; and Group D, polypeptide or fragment thereof is acknowledged. The applicant has amended claims 1 and 27 to limit the scope of claims to an angiogenesis/Axl polypeptide where the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEQ ID NO: 4 and the angiogenesis/Axl polypeptide has kinase activity. Applicant has amended claim 19 to depend from claim 1 and applicant has amended claim 45 to depend from claim 27.

Upon review and reconsideration, given the above amendments, claims 19 and 45 will be rejoined to the elected Group I. The claims will be examined as drawn to *in vitro* as the location for a method for identifying a compound, as well as chemical, phenotypic, or physical effects and compounds wherein the compound is an antibody, antisense molecule, RNAi molecule, small organic molecule. Given that there is no distinction given between a chemical or phenotypic effect in the specification, it will be assumed for examination purposes that chemical or phenotypic effects are the same effects.

Applicant's traversal to the restriction requirement is on the grounds that a search and examination of the claims would not impose a serious burden on the examiner.

The election requirement for Group A is maintained because MPEP 802.01 provides that restriction is proper between inventions that are independent or distinct.

The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. For example, methods drawn to *in vitro* assays do not require the use of animals like *in vivo* assays, which require different methods and techniques than those of *in vitro* assays. Thus different searches and issues are involved in the examination of each species. For these reasons the election requirement is deemed to be proper with regard to species group A and is therefore made FINAL.

2. Claims 1-19, 27-45, 53, and 54 are pending.

3. Claims 13, 38 and 39 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-12, 14-19, 27-37, 40-45, 53, and 54 are currently under consideration.

Claim Objections

6. Claims 19 and 45 are objected to because of the following informalities: The single step is still marked as (iii). Removal of (iii) would obviate this objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-12, 14-19, 27-37, 40-45, 53, and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 cites the limitation "the method of claim 10, wherein the polypeptide is expressed in a eukaryotic host cell". There is insufficient antecedent basis for this limitation in the claim. The correction of this claim to refer to antecedent claim would obviate this rejection.

Claims 1-12, 14-19, 53, and 54 are indefinite because claim 1 does not contain a positive process step which clearly relates back to the preamble.

Claims 27-37, 40-45, 53, and 54 are indefinite because claim 27 does not contain a positive process step which clearly relates back to the preamble.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-12, 14-19, 53, and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that modulates angiogenesis, the method comprising the steps of: (i) contacting the compound with a polypeptide comprising the Axl polypeptide, wherein the Axl polypeptide comprises the amino acid sequence of SEQ ID NO: 4, wherein the Axl polypeptide has kinase activity and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide, does not reasonably provide enablement for a method for identifying a compound that modulates angiogenesis, the method comprising the steps of: (i) contacting the compound with an

angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 or comprises SEQ ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method for identifying a compound that modulates angiogenesis, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEO ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the angiogenesis polypeptide.

This means that the claims encompass a method for identifying a compound that modulates angiogenesis using any angiogenesis polypeptide and wherein the angiogenesis polypeptide has kinase activity. It is noted that the specification defines an angiogenesis polypeptide as polypeptide polymorphic variants, alleles, mutants, and interspecies homologs that: (1) have an amino acid sequence that has greater than about 60% amino acid sequence identity, 65%, 70%, 75%, 80%, 85%, 90%, preferably 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or greater amino acid sequence identity, preferably over a region of over a region of at least about 25, 50, 100, 200, 500, 1000, or more amino acids, to a polypeptide encoded by a referenced nucleic acid or an amino acid sequence, para. bridging p. 7 and 8. Further the claims are drawn to an "angiogenesis polypeptide" which comprises an (emphasis added) amino acid

sequence, which clearly reads on a partial sequence. Thus, the claims read on any polypeptide that comprises 60% of a 25 amino acid sequence fragment of SEQ ID NO: 4 that has kinase activity.

The specification further teaches that the term percent "identity" includes sequences that have deletions and/or additions, as well as those that have substitutions. The specification teaches that, preferably, identity exists over a region that is at least about 25 amino acids in length, or more preferably over a region that is 50-100 amino acids in length, see para. bridging p.3 and 4 of amendment to the specification dated August 20, 2004.

The specification teaches that a functional genetic screening strategy was used to identify proteins involved in regulating endothelial cell migration on specific matrix components, e.g. vitronectin, by stably expressing complex libraries of various types of genetic elements (e.g. cDNAs and GFP-fusions) in human primary endothelial cells (e.g. HUVECs) with a retroviral-based system, p. 5 lines 3-7. The specification teaches that the migration of activated endothelial cells through a vitronectin-rich provisional matrix is critical to the formation of new blood vessels during angiogenesis and is dependent on adhesion receptors containing alpha V integrins (such as alphaVbeta3 which binds to vitronectin), p. 1, lines 22-25. Using this method cells were selected for impaired haptotaxis, Example 1, p. 48, lines 23-30. The specification teaches in Figure 11 that Axl was identified as an antisense hit in this assay.

The specification teaches that Axl is a receptor tyrosine kinase that possesses transforming activity *in vitro* and that Axl is expressed in the vasculature, e.g., endothelial cells (HUVEC) and VSMC, p. 6, lines 9-12. Further the specification teaches that Axl is upregulated in VSMC after vascular injury, p. 6, line 14.

One cannot extrapolate the teachings of the specification to the scope of the claims in view of the teachings of the specification that an angiogenesis polypeptide is only required to have 60% amino acid sequence identity over at least about 25 amino acids of SEQ ID NO: 4 and have kinase activity and can include numerous types of polypeptide variants and that an Axl polypeptide of greater than 90% identity need only have identity over a region of 25 amino acids in length and this includes sequences that have various amino acid changes, because there are no teachings in the specification that the variant polypeptides will function as claimed, i.e. as an angiogenesis polypeptide that has kinase activity. The function of the claimed angiogenesis polypeptide cannot be predicted given the teachings of the specification and the art of record. O'Bryan et al. (Molecular and Cellular Biology, the consensus 1991, 11: 5016-5031) teaches that sequence of the tyrosine kinase domain of Axl contains over 200 amino acids conserved with other tyrosine kinases, see Fig. 3C, p. 5023. Thus, an angiogenesis polypeptide with 60% sequence identity over 25 amino acids (13-14 amino acids) comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEQ ID NO: 4 (15 amino acids X 0.9 = 13-14 amino acids) cannot reasonably be predicted to function as angiogenesis polypeptide that has kinase activity as claimed since neither the specification not the art of record teaches how to make the claimed polypeptide wherein the polypeptide retains only 15 amino acids (60% of 25 amino acids) of SEQ ID NO: 4.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of

predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In view of the unlimited and undefined alteration in the angiogenesis polypeptide contemplated in the specification and claimed, the function of the broadly claimed angiogenesis polypeptide would not be expected to be the same as that of an unaltered angiogenesis polypeptide with kinase activity and the effects of modulators of the claimed protein could not be extrapolated to effects on SEQ ID NO: 4 with a reasonable expectation of success.

Clearly, given the teachings of Bowie et al, Lazar et al, and Burgess et al the effects of undefined changes in the kinase activity of an angiogenesis polypeptide comprising an Axl polypeptide wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEQ ID NO: 4 over 25 amino acids and wherein the angiogenesis polypeptide has kinase activity could not be predicted. Thus, it would take undue experimentation for one of ordinary skill in the art to practice the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will

function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

9. Claims 27-37, 40, 44, 45, 53, and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for identifying a compound that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 or wherein the Axl polypeptide comprises SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide.

The claims encompass a method for identifying a compound that will be effective in modulating tumorigenesis by determining the functional effect of the compound on an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 or wherein the Axl polypeptide comprises SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity.

The specification teaches that a functional genetic screening strategy was used to identify proteins involved in regulating endothelial cell migration on specific matrix components, e.g. vitronectin by stably expressing complex libraries of various types of genetic elements (e.g. cDNAs and GFP-fusions) in human primary endothelial cells (e.g. HUVECs) with a retroviral-

based system, p. 5 lines 3-7. Using this method cells were selected for impaired haptotaxis, Example 1, p. 48, lines 23-30. The specification teaches in Figure 11 that Axl was identified as an antisense hit in this assay.

The specification teaches that Axl is a receptor tyrosine kinase that possesses transforming activity *in vitro* and that Axl is activated by its ligand, Gas 6. The specification teaches that Gas6-Axl interactions stimulate cell survival and chemotaxis. The specification further teaches that Axl is associated with several diseases including rheumatoid arthritis, endometriosis, cancer, e.g. myeloid leukemias such as AML and CML, thyroid carcinomas, and breast cancer, see p. 6, lines 11-19.

Given the teachings of the specification on cancer and tumorigenesis it is clear that claims 27-40, 44, 45, 53, and 54 are drawn to identifying antitumor therapeutics.

One cannot extrapolate the teaching of the specification to enablement of the claims because, although it is known in the art that Axl is associated with tumors and tumor cell transformation, neither the specification nor the art of records provides any nexus drawn to Axl and antitumor therapeutics *in vivo*.

In particular, it is well known that the art of anti-cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that since formal screening for cancer therapeutics began in 1955, although many thousands of drugs have shown activity in either cell or animal models, only 39 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.).

Furthermore, Jain discloses the art known *in vivo* barriers to the delivery of drugs into solid tumors, which have to be overcome for a successful antitumor therapies (Scientific

American July 1994). Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

Thus one cannot predict based on the specification and the art of record that the claimed method would be able to identify a compound that modulates tumorigenesis given the known difficulties in the art in the development and delivery of anti-cancer therapeutics. Thus, undue experimentation by one of ordinary skill in the art would be necessary to practice the method as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as

originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

10. If applicant were able to overcome the rejection set forth above, claims 27-37, 40-45, and 53 would be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that **inhibits** tumorigenesis, the method comprising the steps of: (i) contacting the compound with the Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence of SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide, does not reasonably provide enablement a method for identifying a

compound that **modulates** tumorigenesis, the method comprising the steps of: (i) contacting the compound with the Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence of SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide.

The claims are broadly drawn to a method for identifying a compound that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, and (ii) determining the functional effect of the compound upon the Axl polypeptide.

This means that the claimed method can identify a compound that increases or decreases tumorigenesis.

The specification teaches that Axl is a receptor tyrosine kinase that possesses transforming activity *in vitro* and that Axl is activated by its ligand, Gas 6. The specification further teaches that Gas6-Axl interactions stimulate cell survival and chemotaxis. The specification further teaches that Axl is associated with several diseases including rheumatoid arthritis, endometriosis, cancer, e.g. myeloid leukemias such as AML and CML, thyroid carcinomas, and breast cancer, see p. 6, lines 11-19.

One cannot extrapolate the teachings of the specification to the scope of the claims because Axl is a transforming gene that increases the tumorgenicity of cells, thus the method could not be predictably be used to detect an agent that further increases tumorigencity.

In particular, O'Bryan et al. (Molecular and Cellular Biology, 1991, 11: 5016-5031) teach that Axl was isolated from the DNA of two chronic myelogenous leukemia patients and increases neoplastic transformation of NIH 3T3 cells *in vitro* and *in vivo*, see Abstract, Fig. 5 and

Table 1. However, neither the specification nor art of record teaches the level of Axl required for the stimulation of neoplastic transformation. One cannot reasonably predict for the method as claimed the level of Axl or Axl kinase activity that will transform the cells. Thus, one could not reasonably predict that contacting a compound with an Axl polypeptide would identify a compound that would increase tumorigenesis. Thus it would require undue experimentation for one of ordinary skill in the art to practice the method as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will

function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

11. If applicant were able to overcome the rejection set forth above, claims 27-37, 40-45, and 53 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with the Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence of SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide, does not reasonably provide enablement for a method for identifying a compound that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for identifying a compound that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95 % identity to SEO ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide.

This means that any Axl polypeptide wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 and wherein the Axl polypeptide has kinase activity can be used in the claimed method. Thus, the claims read on an Axl polypeptide wherein the Axl polypeptide comprises 9 amino acids of SEQ ID NO: 4 because 9 amino acids is the smallest whole integer of a polypeptide of 90-95% identity of a given number of amino acids, i.e. 90% or 95% of 10 amino acids = 9 amino acids.

It is noted that the specification teaches that the terms "identical" or percent "identity," in the context of two or more polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues that are the same (i.e., about 70% identity, preferably 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region (e.g., SEO ID NO: 3 or 4), when compared and aligned for maximum correspondence over a comparison window or designated region as measured using a BLAST or BLAST 2.0 sequence comparison algorithms or by manual alignment and visual inspection. The specification teaches that the definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. The specification teaches that, preferably, identity exists over a region that is at least about 25 amino acids in length, or more preferably over a region that is 50-100 amino acids in length, see para. bridging p. 3 and 4 of amendment to the specification dated August 20, 2004. Further it is noted the claims are drawn to an Axl polypeptide, wherein the Axl polypeptide comprises amino acid sequence with greater than 90% or 95% identity to an (emphasis added) amino acid sequence of SEQ ID NO: 4 which reads, for example, on a polypeptide comprising 9 amino acids of SEQ ID NO: 4 that has kinase activity.

The specification teaches that Axl is a receptor tyrosine kinase that possesses transforming activity *in vitro* and that Axl is activated by its ligand, Gas 6. The specification further teaches that Gas6-Axl interactions stimulate cell survival and chemotaxis. The specification further teaches that Axl is associated with several diseases including rheumatoid arthritis, endometriosis, cancer, e.g. myeloid leukemias such as AML and CML, thyroid carcinomas, and breast cancer, see p. 6, lines 11-19.

One cannot extrapolate the teachings of the specification to the scope of the claims in view of the teachings of the specification that an Axl polypeptide of greater than 90% identity which reads, for example, on a polypeptide comprising 9 amino acids of SEQ ID NO: 4 that has kinase activity and can include sequences with numerous types of amino acid sequence changes, because there are no teachings that the variant polypeptides will function as claimed, i.e. as an Axl polypeptide that has kinase activity because the effect of unknown and undefined changes in the Axl polypeptide wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEQ ID NO: 4 cannot be predicted given the teachings of the specification and the art of record. O'Bryan et al. (Molecular and Cellular Biology, 1991, 11: 5016-5031) teaches that the consensus sequence of the tyrosine kinase domain of Axl contains over 200 amino acids conserved with other tyrosine kinases, see Fig. 3C, p. 5023. Thus, a polypeptide sequence with only 90% identity to SEQ ID NO: 4 (~9 amino acids) cannot reasonably be predicted to function as an Axl polypeptide that has kinase activity as claimed.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to

function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In view of the unlimited and undefined alterations in the Axl polypeptide contemplated in the specification and claimed, the function of an altered Axl would not be expected to be the same as that of the unaltered Axl polypeptide and the effects of modulating the claimed protein could not be extrapolated to effects on SEQ ID NO: 4 with a reasonable expectation of success.

Clearly, given the teachings of Bowie et al, Lazar et al, and Burgess et al, the effects of unlimited and undefined changes in an Axl polypeptide could not be predicted. Thus it would require undue experimentation for one of ordinary skill in the art to practice the method as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

12. Claims 1-12, 14-19, 27-37, 40-44, 45 and 53 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-12, 14-19, 27-37, 40-45 and 53 are drawn to methods for identifying compounds that modulate angiogenesis or tumorigenesis, the methods comprising the step of: contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity (for the method of claim 1) or contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 and wherein the Axl polypeptide has kinase activity (for the method of claim 27). Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features

> commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics.... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not

adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the angiogenesis polypeptide or the Axl polypeptide, per Lilly by structurally describing a representative number of angiogenesis polypeptides or the Axl polypeptides or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the angiogenesis polypeptide or the Axl polypeptide required to practice the method of claim 1 or claim 27 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any the angiogenesis polypeptide or the Axl polypeptide, nor does the specification provide any partial structure of such the angiogenesis polypeptide or the Axl polypeptide, nor any physical or chemical characteristics of the angiogenesis polypeptide or the Axl polypeptide nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses two angiogenesis /Axl polypeptides, SEQ ID NOs: 4 and 6 (see Sequence Listing), this does not provide a description of the angiogenesis polypeptide or the Axl polypeptide that would satisfy the standard set out in Enzo.

The specification also fails to describe the angiogenesis polypeptide or the Axl polypeptide by the test set out in Lilly. The specification describes only two angiogenesis /Axl

polypeptides. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of angiogenesis polypeptide or the Axl polypeptide that is required to practice the claimed invention. Since the specification fails to adequately describe the angiogenesis polypeptide or the Axl polypeptide, it also fails to adequately describe the methods for identifying a compound that modulates angiogenesis or tumorigenesis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 2, 5, 6, 9-11, 14, 19, 53, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Healy et al. (Am. J. of Physiology, Lung Cell Molecular Physiology, June, 2001 280: L1273-L1281).

The claims are drawn to a method for identifying a compound that modulates angiogenesis, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEQ ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the functional effect of the

compound upon the angiogenesis polypeptide (claim1), the method of claim 1, wherein the functional effect is determined in vitro (claim 2), the method of claim 2, wherein the functional effect is a chemical effect (claim 5), the method of claim1, wherein the polypeptide is expressed in a eukaryotic host cells (claim 6), the method of claim 1, wherein the functional effect is a chemical or phenotypic effect (claim 9), the method of claim 10, wherein the polypeptide is expressed in a eukaryotic host cell (claim 10), the method of claim 10, wherein the host cell is an endothelial cell (claim 11), the method of claim1, wherein the polypeptide is recombinant (claim 14), and the method of claim 1 further comprising the step of: determining the chemical or phenotypeic effect of the compound upon a cell comprising the angiogenesis polypeptide or fragment thereof thereby identifying a compound that modulates angiogenesis (claim 19), the method of claim 1 or 27 wherein the Axl polypeptide comprises an amino acid sequence greater than 95% identity to SEQ ID NO: 4 (claim 53), and the method of claim 53 wherein the Axl polypeptide comprises SEQ ID NO: 4 (claim 54).

It is assumed for examination purposes for the reasons stated above in the rejection under U.S.C. 112 first paragraph that an Axl polypeptide wherein the Axl polypeptide comprises an amino acid sequence great than 90 or 95% identity to SEQ ID NO means a polypeptide of at least 9 amino acids of SEQ ID NO: 4 that has kinase activity.

It is noted that the specification teaches that the phrase "functional effects" in the context of assays for testing compounds that modulate activity of an angiogenesis and tumorigenesis protein includes the determination of a parameter that is indirectly or directly under the influence of an angiogenesis polypeptide, e.g., a chemical or phenotypic effect such as loss-of angiogenesis or tumorigenesis phenotype represented by a change in expression of a cell surface

marker αVβ3 integrin, changes in cellular migration, changes in endothelial tube formation, and changes in tumor growth, or changes in cellular proliferation, especially endothelial cell proliferation; or enzymatic activity; or, e.g., a physical effect such as ligand binding or inhibition of ligand binding. A functional effect therefore includes ligand binding activity, the ability of cells to proliferate, expression in cells undergoing angiogenesis or tumorigenesis, and other characteristics of angiogenic and tumorigenic cells. "Functional effects" include in vitro, in vivo, and ex vivo activities, p. 8, lines 15-26. Additionally, it is noted that the specification teaches that "determining the functional effect" means assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis protein, e.g., measuring physical and chemical or phenotypic effects. Such functional effects can be measured by any means known to those skilled in the art including measuring apoptosis and cell cycle arrest, para. bridging, p. 8 and 9.

Given that there is no distinction given between a chemical or phenotypic effect in the specification, it will be assumed for examination purposes that chemical or phenotypic effects are the same effects.

Healy et al. teach a method for identifying a compound (Gas-6) that modulates angiogenesis, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, as defined by the specification (see above and para. bridging p. 7 and 8 of the specification), wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95 % identity to SEQ ID NO: 4 or comprises SEQ ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the functional (chemical) effect of the compound upon the angiogenesis polypeptide

by contacting human pulmonary endothelial cells (eukaryotic cells) that express human Axl (see Fig. 2) with the Axl ligand Gas 6 and determining the effect of this interaction on cell number, see Abstract, p. 1276, left column, and Fig. 6. Healy et al. teach measuring the chemical effect of Gas 6 on human pulmonary endothelial cells overexpressing Axl by determining the level of apoptosis in said cells, see Abstract and Fig. 9 and 10.

Although the reference does not specifically that the Axl of the reference is SEQ ID NO: 4 given that the Axl polypeptide of SEQ ID NO: 4 and Healy et al. are human Axl, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best, 562 F2nd 1252, 195 USPQ 430 (CCPA 1977).

14. Claims 27-37, 44, 45, 53, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Varnum, et al. (Nature, February 16, 1994, 373:623-626), as evidenced by ATCC number CRL-1620, cell line A-172 (www.atcc.org), as further evidenced by Sigma-Aldrich Catalog number V3501, Vitamin K_1 (www.sigma-aldrich.com).

The claims are drawn to a method for identifying a compound that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than

90% identity to SEO ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide (claim 27), the method of claim 27, wherein the functional effect is determined in vitro (claim 28), the method of claim 28, wherein the functional effect is a physical effect (claim 29), the method of claim 28, wherein the functional effect is determined by measuring ligand binding to the polypeptide (claim 30), the method of claim 28, wherein the functional effect is a chemical effect (claim 31), the method of claim 27, wherein the polypeptide is expressed in a eukaryotic host cell (claim 32), the method of claim 27, wherein the functional effect is a physical effect (claim 33), the method of claim 33, wherein the functional effect is determined by measuring ligand binding to the polypeptide (claim 34), the method of claim 27, wherein the functional effect is a chemical or phenotypic effect (claim 35), the method of claim 35, wherein the polypeptide is expressed in a eukaryotic host cell (claim 36), the method of claim 35, wherein the host cell is a cancer cell (claim 37), the method of claim 27, wherein the compound is a small organic molecule (claim 44), the method of claim 27, further comprising the step of determining the chemical or phenotypic effect of the compound upon a cell comprising the Axl polypeptide or fragment thereof, thereby identifying a compound that modulates tumorigenesis (claim 45), the method of claim 1 or 27 wherein the Axl polypeptide comprises an amino acid sequence great than 95% identity to SEQ ID NO: 4 (claim 53), and the method of claim 53 wherein the Axl polypeptide comprises SEQ ID NO: 4 (claim 54).

It is assumed for examination purposes for the reasons stated above in the rejection under U.S.C. 112 first paragraph that an Axl polypeptide wherein the Axl polypeptide comprises an

amino acid sequence great than 90 or 95% identity to SEQ ID NO means a polypeptide of at least 9 amino acids of SEQ ID NO: 4 that has kinase activity.

It is further noted, in addition to the description of "functional effect" and "determining the functional effect" described above, the specification teaches that a "small organic molecule" refers to an organic molecule, either naturally occurring or synthetic, that has a molecular weight of more than about 50 daltons and less than about 2500 daltons, preferably less than about 2000 daltons, preferably between about 100 to about 1000 daltons, more preferably between about 200 to about 500 daltons.

ATCC number CRL-1620 teaches that the A-172 cell line is human, eukaryotic, glioblastoma cancer cell line and Sigma-Aldrich Catalog number V3501, Vitamin K_1 teaches that is a small organic molecule.

Varnum, et al. (Nature, February 16, 1994, 373:623-626), teach a method for identifying a compound (Gas 6 or vitamin-K) that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEQ ID NO: 4 or comprises SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity (Fig: 1 and 3) and (ii) determining the functional effect of the compound upon the Axl polypeptide wherein the functional effect is determined *in vitro* by measuring the functional, physical effect of ligand binding by treating A172 cells, which comprise human Axl (see Fig. 1) with Gas6 alone or conditioned media containing Gas6 and vitamin K and measuring ligand binding to Axl as measured by downregulation of Axl (p. 624, top left para., Fig. 3b-c). Ligand binding of Gas6 to Axl on A172 cells was also determined by measuring the amount of ^{125}I-Gas6 binding to Axl on

A172 cells, see Fig. 4. Varnum, et al. also teach determining a functional, chemical effect by treating A-172 cells with Gas6 and measuring the kinase activity of Axl, see p. 623, left column and Figs. 1a and 3a.

The method of the prior art comprises the same method steps as claimed in the instant invention, that is (i) contacting a compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEQ ID NO: 4 or comprises SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity and (ii) determining the functional effect of the compound upon the Axl polypeptide to the same population of cells, cancer cells, thus the claimed method is anticipated because the method will inherently lead to identifying a compound that modulates tumorigenesis, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Although the reference does not specifically that the Axl of the reference is SEQ ID NO: 4 given that the Axl polypeptide of SEQ ID NO: 4 is human and the A-172 cells are human, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best, 562 F2nd 1252, 195 USPQ 430 (CCPA 1977).

Furthermore, although the reference does not specifically state that the Vitamin K was still present in the conditioned media contacting the Axl polypeptide, the claimed method

appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the small organic molecule of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the prior art and to establish patentable differences. See In re Best, 562 F2nd 1252, 195 USPQ 430 (CCPA 1977).

15. Claims 27 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee, et al. (Molecular and Cellular Biology, December, 1999, 19: 8075-8082)

The claims are drawn to a method for identifying a compound that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEO ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide (claim 27), the method of claim 27, wherein the polypeptide is recombinant (claim 40).

It is assumed for examination purposes for the reasons stated above in the rejection under U.S.C. 112 first paragraph that an Axl polypeptide wherein the Axl polypeptide comprises an amino acid sequence great than 90 means a polypeptide of at least 9 amino acids of SEQ ID NO: 4 that has kinase activity.

It is again noted that the specification teaches that the phrase "functional effects" in the context of assays for testing compounds that modulate activity of an angiogenesis and tumorigenesis protein includes the determination of a parameter that is indirectly or directly

under the influence of an angiogenesis polypeptide, e.g., a chemical or phenotypic effect such as loss-of angiogenesis or tumorigenesis phenotype represented by a change in expression of a cell surface marker αvβ3 integrin, changes in cellular migration, changes in endothelial tube formation, and changes in tumor growth, or changes in cellular proliferation, especially endothelial cell proliferation; or enzymatic activity; or, e.g., a physical effect such as ligand binding or inhibition of ligand binding. A functional effect therefore includes ligand binding activity, the ability of cells to proliferate, expression in cells undergoing angiogenesis or tumorigenesis, and other characteristics of angiogenic and tumorigenic cells. "Functional effects" include in vitro, in vivo, and ex vivo activities, p. 8, lines 15-26. Additionally, it is noted that the specification teaches that "determining the functional effect" means assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis protein, e.g., measuring physical and chemical or phenotypic effects. Such functional effects can be measured by any means known to those skilled in the art, p.8, lines 27-30.

Lee et al. teach a method for identifying a compound (Gas 6) that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity; and (ii) determining the functional effect of the compound upon the Axl polypeptide wherein the polypeptide is recombinant by determining the functional chemical effects of Gas-6 on human ovarian cancer cells expressing recombinant Axl (see Fig. 3 and Materials and Methods, p. 8077, left column) by measuring Axl activation/phosphorylation (Fig. 4B and D, p. 8078, right

column), mitogenesis (Fig. 4C, p. 8078, right column) and apoptosis (Fig. 5, p. 8079, bottom of page), also see Abstract.

The method of the prior art comprises the same method steps as claimed in the instant invention, that is (i) contacting a compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% identity to SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity and (ii) determining the functional effect of the compound upon the Axl polypeptide to the same population of cells, cancer cells, thus the claimed method is anticipated because the method will inherently lead to identifying a compound that modulates tumorigenesis, See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Although the reference does not specifically teach that the Axl of the reference is SEQ ID NO: 4 given that the Axl polypeptide of SEQ ID NO: 4 is human and the recombinant Axl was isolated from human cells (see cloning of the band of interest revealed by the tyrosine kinase display assay, p. 8076 and ATCC Number: HTB-77 (www.atcc.org)), the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best, 562 F2nd 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 12, 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Healy et al. (Am. J. of Physiology, Lung Cell Molecular Physiology, June, 2001 280: L1273-L1281) as applied to claims 1, 2, 5, 6, 9-11, 14, 19, 53, and 54, above, in view of Varner and Cheresh (Current Opinion in Cell Biology, October 1996, 8:724-730) in further view of Panzer et al. (United States Patent Application, 20040048253, February 21, 2001), and in further view of Ruoslahti et al (US Patent 6,180,084 January, 2001). -IDS-PJR

The claims are drawn to the method of claim 11 wherein the functional effect is determined by measuring αVβ3 expression or haptotaxis (claim 12), the method of claim 1, wherein the compound is an antibody (claim 15), the method of claim 1, wherein the compound is an antisense molecule (claim 16), the method of claim 1, wherein the compound is an RNAi molecule (claim 17) and the method of claim 1, wherein the compound is a small organic molecule (claim 18).

Healy et al. teach a method for identifying a compound (Gas-6) that modulates angiogenesis, the method comprising the steps of: (i) contacting the compound with an angiogenesis polypeptide comprising an Axl polypeptide, as defined by the specification (see above and para. bridging p. 7 and 8 of the specification), wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95 % identity to SEQ ID NO: 4 or comprises SEQ ID NO: 4 and wherein the angiogenesis polypeptide has kinase activity; and (ii) determining the functional (chemical) effect of the compound upon the angiogenesis polypeptide by contacting human pulmonary endothelial cells (eukaryotic cells) that express human Axl (see Fig. 2) with the Axl ligand Gas 6 and determining the effect of this interaction on cell number, see Abstract, p. 1276, left column, and Fig. 6. Healy et al. teach measuring the chemical effect

of Gas 6 on human pulmonary endothelial cells overexpressing Axl by determining the level of apoptosis in said cells, see Abstract and Fig. 9 and 10.

Healy et al. do not teach determining the functional effect by measuring αVβ3 expression or haptotaxis or the use of an antibody, an antisense molecule, an RNAi molecule, or a small organic molecule.

Varner and Chersh teach that integrin αVβ3 is significantly upregulated on vascular cells within human tumors and in response to growth factors and plays a biological role in a critical event of blood vessel formation during tumor angiogenesis, see section on Role of Integrins in Tumor Angigogenesis, p. 726- 727.

Panzer et al. teach the common art practice of screening small molecules, antibodies, oligonucleotides, and the antisense molecules for use in diagnosis and therapies, see para 0735-0741 and 0754-0757of the published application. Similarly Ruoslahti et al teach the common art practice of screening organic chemicals, nucleic acid molecules such as RNA, a cDNA, or oligonucleotides, and antibodies for use in therapies, see Col 1, 2, 9-12.

Thus it would have been *prima facie* obvious at the time the invention was made to perform the method of claim1 by measuring αVβ3 expression and to use an antibody, antisense molecule, RNAi, or small organic molecule as the compound to use in the screening method because the level αVβ3 expression was known to be important in angiogenesis and the screening of various modulatory compounds for therapeutic purposes was conventionally used in the art at the time of the invention. Thus one of ordinary skill in the art would have had motivation and a reasonable expectation of success in making and using the claimed invention.

18. Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Varnum et al. (Nature, February 16, 1994, 373:623-626) as applied to claims 27-37, 44, 45, 53, and 54, above, in further view of Panzer et al. (United States Patent Application, 20040048253, February 21, 2001), and in further view of Ruoslahti et al (US Patent 6,180,084 January, 2001). IDS-PTO

The claims are drawn to the method of claim 27, wherein the compound is an antibody (claim 41), the method of claim 1, wherein the compound is an antisense molecule (claim 42), and the method of claim 1, wherein the compound is an RNAi molecule (claim 43).

Varnum, et al. (Nature, February 16, 1994, 373:623-626), teach a method, as described above, for identifying a compound (Gas 6 or vitamin-K) that modulates tumorigenesis, the method comprising the steps of: (i) contacting the compound with an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 90% or 95% identity to SEO ID NO: 4 or comprises SEQ ID NO: 4 and wherein the Axl polypeptide has kinase activity (Fig: 1 and 3) and (ii) determining the functional effect of the compound upon the Axl polypeptide, the method of claim 27, wherein the functional effect is determined *in vitro* by measuring the functional, physical effect of ligand binding by treating A172 cells, which comprise human Axl (see Fig. 1) with Gas6 alone or conditioned media containing Gas6 and vitamin K and measuring ligand binding to Axl as measured by downregulation of Axl (p. 624, top left para., Fig. 3b-c). Ligand binding of Gas6 to Axl on A172 cells was also determined by measuring the amount of ^{125}I-Gas6 binding to Axl on A172 cells, see Fig. 4. Varnum, et al. determined a functional, chemical effect by treating A-172 cells with Gas6 and measuring the kinase activity of Axl, see p. 623, left column and Figs. 1a and 3a.

Varnum et al do not teach using an antibody, an antisense molecule, or an RNAi molecule as the modulatory compound.

Panzer et al. teach the common art practice of screening small molecules, antibodies, oligonucleotides, and the antisense molecules for use in diagnosis and therapies, see para 0735-0741 and 0754-0757of the published application. Similarly Ruoslahti et al teach the common art practice of screening organic chemicals, nucleic acid molecules such as RNA, a cDNA, or oligonucleotides, and antibodies for use in therapies, see Col 1, 2, 9-12.

Thus it would have been *prima facie* obvious at the time the invention was made to use an antibody, antisense molecule, RNAi, or small organic molecule as the compound to use in the screening method because the screening of various modulatory compounds for therapeutic purposes was conventionally used in the art at the time of the invention. Thus one of ordinary skill in the art would have had motivation and a reasonable expectation of success in making and using the claimed invention.

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR

SUSAN UNGAR, PH.D
PRIMARY EXAMINER